TOX/MIN/2012/04

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Minutes of the meeting held on Tuesday, 26 June 2012 in Aviation House, London.

Present

Chairman:	Professor D Coggon		
Members:	Mr D Bodey		
	Prof J Cade		
	Dr R Dearman		
	Dr M Graham		
	Dr A Hansell		
	Prof R Harrison		
	Prof J Konje		
	Prof B Lake		
	Prof I Morris		
	Dr N Plant		
	Prof R Smith		
	Dr J Thompson		
	Prof F Williams		
Food Standards Agency (FSA) Secretariat:	Dr D Benford	Scientific Secretary	
	Mrs J Shroff	Administrative Secretary	
	Ms R Acheampong		
	Dr C Baskaran		
	Dr E Cemeli		
	Mr T Chandler		
	Dr D Gott		
	Ms F Hill		
	Dr M Kurzawa-Zegota		
	Ms C Mulholland		
	Dr D Parker		
	Ms C Potter		
	Dr J Shavila		
Health Protection Agency (HPA) Secretariat:	Mr J Battershill	Scientific Secretary	
	Ms F Pollitt		
Invited Expert	Prof P J Aggett	SACN	
Officials:	Dr A Tedstone	Department of Health	Items 4,5
	Dr J Buck	FSA, Food Allergy Branch	Item 5
	Ms N Golden	FSA, Press Office	
Assessors	Ms M Benton	Health & Safety Executive	
	Mr C Powlesland	Environment Agency	

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Announcements

1. The Chairman, Professor Coggon, welcomed Members to the meeting.

2. The Chairman also welcomed Prof Peter Aggett (Member of the Scientific Advisory Committee on Nutrition (SACN)), and Dr Alison Tedstone (Department of Health) who were present to contribute to discussion on items 4 and 5, and Dr Joelle Buck from the Food Allergens Branch of the Chemical Safety Division of the FSA (present to contribute to discussion of item 5).

3. The Chairman informed Members that the FSA wished to appoint an expert member to join the General Advisory Committee on Science (GACS). The Agency was particularly keen to hear from applicants with expertise in nutrition. He asked Members to draw the vacancy to the attention of colleagues who might be interested. Completed applications had to be received by Wednesday 4 July 2012. Full details of the position, including criteria required for appointment, were set out in an application pack available on the FSA website.

4. The Chairman drew Members' attention to a recent publication of findings from the Heidelberg arm of the European Prospective Investigation of Cancer (EPIC)[1], which had indicated that calcium supplementation might increase the risk of myocardial infarction, and had attracted some media interest. He thanked Professor Cade who had commented on the paper at short notice. As calcium supplementation had been associated with a similar elevation of risk in earlier work by Bolland *et al*, the Chairman suggested that it might be timely to review the possible effects of high intakes of calcium and risk of myocardial infarction. Members agreed, and noted that because the relevant database was extensive, it was likely that this would be done in 2013.

5. The Chairman reminded those attending the meeting to declare any commercial or other interests that they might have in any of the agenda items.

Item 1: Apologies for absence

6. Apologies for absence were received from Drs Brimblecombe and Foster and Professors D Harrison and B Houston. Written comments were received from one Member.

Item 2: Draft minutes of the meeting held on Tuesday, 8th May 2012 – TOX/MIN/2012/03

[1] Li K, Kaaks R, Linseisen J, Rohrmann S. (2012). Heart. 98(12):920-5

7. The minutes of the 8th May 2012 meeting were agreed subject to the following amendments (in italics):

- Para 8, page 5, line 3: ~~A member reported that the Small Area Health Statistics Unit. (SAHSU) at Imperial College London was discussing use and understanding of numbers.~~ Members noted.....

Para 12, line 4: ... the review needed to consider maternal diet *during pregnancy as well as during breastfeeding*, whereas for ~~the~~ chemical toxicity, only the infant diet *(including breast milk)* needed to be considered.

Para 45, line 3: However, *it was suggested that* some of the examples given in the opinion were not correct*ly presented* ~~mathematically~~.

Item 3: Matters arising

8. *Matters arising from the meeting of 8th May 2012*

- Para 10: The annual report of the COT/COC/COM had been completed and would be published on their websites shortly.

- Para 51: The Secretariat would write to the representatives of the United States Agencies, thanking them for helpful information on toxicogenomics, once a near-final draft of the statement was available.

- Para 57: The Committee had requested input from the FSA's Social Science Research Unit on the impact of the marketing techniques used by the manufacturers of energy drinks and the effects they might have on consumption patterns and behaviour. This had been received and would be discussed later under Item 7 of the agenda.

- Para 59: Dr Benford gave a verbal report on the workshop on uncertainty held by the Interdepartmental Group on Health Risks from Chemicals (IGHRC), which had been attended by officials of different departments and agencies. She had provided the COT's conclusions on this subject (discussed at the meeting on 8th May 2012) to the workshop participants. She briefly described some exercises on uncertainty that had been carried out. The IGHRC aimed to produce a document on different ways of dealing with uncertainty, but this would not be prescriptive. A new Member expressed his interest in the topic and would be sent links to the previous COT papers.

9. Item 4: With regard to food allergens in the infant diet, Dr Tedstone elaborated on the objectives of the SACN review of complementary and young child feeding, for which the COT were being asked to undertake a review of the literature on infant diet and risks relating to the development of allergic disease. She explained that the specific areas upon which SACN were looking for the COT review to focus were:

- Risks of sensitisation to allergens that may be present in the infant diet

- Risks of atopic disease more generally in relation to the infant diet

- Risks of autoimmune disease in relation to the infant diet (Members noted that the recent joint COT-SACN work on gluten would not be duplicated).

10. It had previously been proposed to exclude from the review evidence relating to the timing of introduction of complementary and/or specific foods into the infant diet and the risk of developing atopic disease, because of major randomised controlled trials (RCTs) on the question that were currently ongoing. However, this was an important topic and because of the need to provide advice to SACN within the timeframe of the SACN review, it was now decided that a review of currently available evidence would be included within the scope of the review. The conclusions would then be revisited at a later stage (likely to be after 2015) when the two ongoing RCTs in the UK had been completed. It was confirmed that effects of infant diet on risk of autoimmune disease would also be covered.

11. It was decided that whilst the focus of the review would be on risks arising from the infant diet, it would be necessary as part of this, to consider the potential confounding influence of maternal diet (during pregnancy and/or postnatally while breastfeeding).

12. It was suggested that the review should be based primarily on prospective human studies and RCTs, and that other types of evidence should be considered only where routes of exposure were relevant and where dietary data were robust. Regarding the influence of gut microflora, Members considered that while there were a lot of claims relating to prebiotics and probiotics, there was not likely to be much hard evidence on subsequent risk of allergy.

13. In addition to input from three external experts who had been chosen to assist the COT with their consideration of this topic, an external research team would be commissioned to find and summarise the relevant literature. Several Members of the COT would provide comments on the draft specification for tender (provided they had no conflict of interest). Since the tender was expected to go out in the summer, this would be done as soon as possible. The Committee also agreed to provide input on the way the work should be taken forward once the tender had been awarded to a contractor.

Item 4: SACN Review of vitamin D. Adverse effects of high levels - TOX/2012/23

14. The Scientific Advisory Committee on Nutrition (SACN) was in the process of reviewing its recommendations on vitamin D, and the COT had been asked to advise on possible adverse effects of high levels of vitamin D intake. An introductory paper (TOX/2011/19) had been considered by the Committee in June 2011.

15. At that meeting it had been agreed that both human and animal data should be considered, and that it might be necessary to assess safety at different levels of vitamin D intake, rather than establish a single tolerable upper level (TUL). It was

agreed also that it might be necessary to consider the relation of adverse effects to specified blood levels of vitamin D as well as to vitamin D intakes.

16. It had further been agreed that a 2011 US Institute of Medicine (IOM) report[2] should be used as a bibliographic source, since it was a very recent publication which included helpful systematic reviews. However additional papers published after the IOM review would also be considered, together with those identified by the Secretariat during the review process as being of particular interest.

17. Members were now provided with a new paper on the topic (TOX/2012/23 and its annexes). It was noted that this would need to be updated to take account of newly available data. Given the large amount of information that was available, it would be important to focus only on that which was relevant to the advice that SACN required. The SACN review would cover all aspects of vitamin D, including the low vitamin D levels which were prevalent in certain population groups.

18. Members were informed that new data on blood levels of vitamin D in the UK population of adults and older children would be available (from the National Diet and Nutrition Survey) by the end of July 2012, with corresponding information for infants in 2013. This would be considered by SACN later in the review process. It was agreed that as the distribution of blood levels would be important to COT's consideration of risks, the information on blood levels that was currently available should be provided in the first instance.

19. It was planned that a draft of the SACN review would be published for public consultation in 2013, and that new information could still be included after that time. Some information was available on the patterns of supplement use and how it had changed over time. Food composition tables might also provide information on vitamin D intakes, although it was noted that there were uncertainties about the methodology of the different vitamin D assays used. Exposure measures had not been standardised, though some validation work was underway.

20. It was agreed to use a single set of units, gravimetric for intakes and molar for serum levels. Members noted that whether calcitriol, the active form of vitamin D, was a hormone was controversial, and agreed that in the context of TULs it should be referred to as a nutrient as its role was to mobilise calcium.

21. Many published studies concerned the effects of supplementation with vitamin D and calcium in combination, making it difficult to discern the separate impact of vitamin D. Where vitamin D and calcium were given together it would be useful to know what doses of calcium were used, since the Committee's interest was in the effects of vitamin D at normal levels of calcium intake. Information on the effects of hypercalcaemia and excess calcium in the absence of vitamin D supplementation had been included in the paper as it should help in deciding what is relevant or important when looking at vitamin D induced hypercalcaemia. While it was useful background, this need not be included in the final report if it did not contribute to the conclusions.

[2] Institute of Medicine, Committee to Review Dietary Reference Intakes for Vitamin and Vitamin D, Food and Nutrition Board (2011). Dietary Reference values for calcium and vitamin D and Fluoride. Available at http://www.nap.edu/catalog/13050.html

22. In the published reports of vitamin D toxicity, it had always been associated with supplementation, fortification or medical treatment, and it appeared not to occur in the general population through normal dietary intake. However, it would be worth considering whether levels of intake could be of concern where infants were given both vitamin drops and also infant formula that was fortified with vitamin D.

23. Data had not been provided on the extent of vitamin D formation from sunlight. This was thought to be subject to greater homeostatic control and the uptake and metabolism via this route differed compared to dietary intake. Vitamin D produced from sunlight entered the circulation directly, whilst vitamin D from food or dietary supplements underwent significant presystemic metabolism in the liver. Cases of vitamin D toxicity attributed only to UV exposure had not been documented. Some studies had attempted to control for sunlight by taking into account the seasons in which blood samples were taken and/or physical activity (presumably as an indicator of time spent outdoors) in their models. SACN would be considering the impact of sunlight on vitamin D status and information would be provided to COT in due course.

24. Little information was available on potential adverse effects of vitamin D intake during pregnancy. There were no case reports relating to pregnancy, and pregnant women were likely to be excluded from clinical trials.

25. Some studies had suggested that vitamin D was less available when Body Mass Index (BMI) was higher. It was noted that the better quality studies corrected for BMI. Members were advised that SACN would be considering the influence of BMI in their review of vitamin D.

26. It was noted that the non-monotonic exposure-response relationships which had been observed for some end-points such as all-cause mortality, had a reverse J-shape rather than a U-shape, with higher risk in the lowest category of serum vitamin D levels than in the highest category. The elevation of risk at higher serum levels might reflect confounding (some types of illness leading to increased serum levels and also predisposing to earlier death), and was not necessarily causal.

27. Members considered that the J-shaped curve described for pancreatic cancer was of interest, but that the suggested relationships for other cancer endpoints were not convincing and that it would not be necessary to refer the question of carcinogenicity to the COC at this time. It was noted that the Medicines and Healthcare products Regulatory Agency (MHRA) were looking at this topic, and in particular at possible interaction between vitamin D and IGFBP-3 in the cell signalling and proliferation processes. This had been observed *in vitro* and while it was possible that it was an artefact, it could also be a real effect. It was suggested that the World Cancer Research Fund (WCRF) continuous update could provide information on vitamin D and cancer.

28. Members agreed that it would be useful to consider the findings of Cochrane reviews on vitamin D, but that care should be taken to ensure that findings from primary research were not “double counted”.

29. It was agreed that hypercalcaemia could be a useful endpoint on which to base a TUL, but that it would be important to distinguish free ionised calcium, which drives toxicity, from total calcium which includes calcium bound to protein. Ionised calcium was under tight regulatory control. Albumin was not saturated and it was likely that bound calcium would predominate. Although, hypercalcuria could be considered as an outcome where it had been measured, it was harder to interpret (unless assessed in 24 hour samples) because of uncertainties about the extent of dilution from concomitant excretion of water. In addition, urinary calcium sometimes increased when serum calcium did not. The balance of blood and urinary calcium might be important.

30. Members doubted whether older people should be considered a potentially vulnerable group because of reduced kidney function. It was noted that kidney disease could reduce the metabolism of vitamin D to its active form, and this would tend to protect against toxicity. No other potentially vulnerable groups were identified. It was unclear if lifetime exposure to high levels of vitamin D increased vulnerability.

31. It was asked whether any genetic polymorphism might be relevant to toxicity. This issue had not been addressed in paper TOX 2012/23, but SACN would be looking at polymorphisms.

32. At present it was not possible to determine whether a TUL could be established either for total or for supplemental intake. Similarly it was not possible to conclude whether vitamin D blood levels or intakes should be used in any advice. Further information would be needed on serum levels and their relationship with intake to draw any conclusions on this.

33. The COT's provisional position would be discussed by the SACN at their September meeting, either as a provisional position paper or as detailed minutes.

Item 5: Second draft over-arching statement on risks of chemicals and the development of food allergic disease, of relevance to infant feeding - TOX/2012/20

34. A second draft over-arching statement was discussed. It aimed to explain why detailed review was not needed for some chemicals at the current time. It also addressed the potential allergenicity of these chemicals, as requested by the Committee during previous discussion, and the Secretariat sought further advice on the approach to be taken when reviewing evidence in this area.

35. Members suggested alterations to improve the clarity of the over-arching statement with respect to its context, and also that tolerable intake levels be specified more clearly so that the implications of estimated exposures could be assessed more easily.

36. The Committee discussed how to refine the approaches used to review the potential allergenicity of the chemicals included in the over-arching statement. Differing information had been retrieved in the initial literature searches. Members clarified that the central issues were 1) whether or not there was any evidence that

the chemical was an allergen itself or triggered allergic symptoms/reactions, and 2) whether oral exposure to the chemical could cause sensitisation. Adjuvant effects were not considered relevant in the context of the present review. It was thought unlikely that any of the chemicals were important sensitisers via the diet. With respect to infant susceptibility, it was noted that there would not be a difference in the agents causing allergy in infants as opposed to adults, but that infants were more likely to develop allergy and could then recover.

37. With regard to the extensive literature available for some of the chemicals, two possible approaches were discussed. Focussing the search more tightly on the areas of interest by adding the terms infant and then diet in a stepwise fashion, was one possibility. A second option was to look for recently published reviews of the chemicals in question, which could be used as the basis for consideration of their allergenicity in this context. Some relevant information might be included in the evaluations leading to establishment of their tolerable intake levels. The Secretariat would consider this further in consultation with a COT Member.

38. It was noted that a paragraph describing the approach that would be taken in reviewing evidence relating to infant diet and risk of atopic disease, would be amended in line with the slightly revised approach agreed for this review under Matters Arising (paragraphs 9 - 13).

39. A third draft of the over-arching statement, addressing the points discussed, would be presented at a subsequent meeting.

Item 6: Review of potential risks from high levels of aluminium in the infant diet - TOX/2012/21

40. During the discussion on complementary and young child feeding in February 2012, Members had requested a more in-depth review on aluminium. Members were provided with paper TOX/2012/21 and were asked to comment on the information in the paper, the estimates of dietary exposure, the impact of nutritional status on aluminium absorption, and requirements for additional information.

41. The Committee requested more detailed information on the absorption of aluminium, including where in the gut absorption took place predominantly, and the impact that other dietary constituents might have on the absorption of aluminium. Further details were also requested on accumulation of aluminium in tissues (brain and bone) in addition to the blood. Studies looking at bioavailability and accumulation needed to be explored further before final conclusions could be drawn. Further information was also requested on comparisons of the bioavailability of aluminium from food and drinking water.

42. Additional clarification on the possibility of neurotoxicity was requested, including a definition of Bayley Mental Development Index scores. It would be helpful for Members to see the monograph describing the establishment of the Provisional Weekly Tolerable Intake (PTWI), by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

43. Members also requested consideration of exposure and absorption from non-food sources, such as through inhalation of dust and ingestion following hand-mouth transfer in infants and toddlers (aluminium silicates).
44. Further refinements to the exposure assessment were needed to reduce the substantial uncertainties. The new Diet and Nutrition Survey of Infants and Young Children (DNSIYC) database might help to provide a more accurate assessment. However, the data would not be available until early 2013. It was suggested that sensitivity analysis be performed on the percentage of the diet from foods with high levels of aluminium.

45. It was agreed that these issues would be addressed and a draft COT statement would be prepared for discussion at a future meeting.

Item 7: First draft statement on the interaction of caffeine and alcohol and their combined effects on health and behaviour - TOX/2012/22

46. At their meeting in March, the Committee had considered a review of the literature on potential interactions between caffeine and alcohol. A draft COT statement had been prepared for consideration at the current meeting.

47. In March, the Committee had expressed an interest in the effects of sugars and artificial sweeteners on gastric emptying and therefore the impact of sugar-sweetened drinks compared to artificially sweetened drinks on peak blood alcohol levels. The Secretariat had provided information demonstrating that mono- and disaccharides consumed in alcoholic mixers slowed gastric emptying and reduced peak blood alcohol levels when compared to artificially sweetened mixers. The Committee concluded that as sales of artificially sweetened (diet) energy drinks were significantly lower than those of energy drinks containing mono- and disaccharides, reference to the effect of sugars and sweeteners on gastric emptying was not necessary in the statement.

48. Following the meeting in March, the Secretariat had requested advice from the Social Sciences Research Unit of the FSA, who had come back with a number of questions regarding gaps in the data. The Committee concluded that the data were not readily available to answer these questions and that research in this area was not covered by the Committee's remit. Members decided not to include a conclusion on the social science aspects of this topic.

49. A number of suggestions were made to improve the statement. A second draft would be prepared for discussion at a future meeting.

Item 8: Draft statement on the use of toxicogenomics in risk assessment - TOX/2012/24

50. Members were provided with a first draft COT statement on the use of toxicogenomics in risk assessment. The Committee suggested modifications in the overall structure and clarifications to the text.

51. The introduction referred to toxicogenomics as the integration of 'omics approaches, but this was not reflected in the rest of the draft statement, which focussed on gene changes. It needed to be clear that this reflected the current state of maturity of the different approaches, and that ultimately the conclusions could also be relevant to proteomics and metabonomics. Specific points that were raised included a need to clarify text relating to biological networks and for the conclusions to be clear about the stages of risk assessment to which toxicogenomics could contribute.

52. The draft statement would be revised for discussion at the September 2012 meeting.

Item 9: FSA Scientific Advisory Committees (SACs) Update - TOX/2012/25

53. Members were provided with a paper outlining the headline topics that other Committees were discussing, and were advised that it would be possible to obtain details on any of the topics if required.

Item 10: Any other business

54. Members were informed that in response to COT advice given in 2007, the Department of Transport (DfT) had commissioned research into the cabin air environment of aircraft. This research had been completed and DfT had referred the results of the studies to the Committee for its consideration. A draft discussion paper would be prepared by the HPA Secretariat in due course.

Item 11: Date of next meeting

55. The next meeting was scheduled to take place on Tuesday 11th September 2012. The venue would be confirmed nearer the date.